General

Guideline Title

The prognostic value of the DNMT3A biomarker in cytogenetically normal patients with acute myeloid leukemia.

Bibliographic Source(s)

Leber B, Ismaila N, Kamel-Reid S, Rutherford M, Molecular Oncology Advisory Committee. The prognostic value of the DNMT3A biomarker in cytogenetically normal patients with acute myeloid leukemia. Toronto (ON): Cancer Care Ontario (CCO); 2013 Nov 27. 17 p. (Recommendation report; no. MOAC-1). [23 references]

Guideline Status

This is the current release of the guideline.

The RECOMMENDATION report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Recommendation

Deoxyribonucleic acid (DNA) methyltransferase 3A (DNMT3A) mutation testing should be included as a biomarker test in cytogenetically normal acute myeloid leukemia (AML) patients.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute myeloid leukemia (AML)

Guideline Category

Evaluation

Risk Assessment

Clinical Specialty

Internal Medicine

Medical Genetics

Oncology

Intended Users

Other

Patients

Physicians

Guideline Objective(s)

To determine if testing for deoxyribonucleic acid (DNA) methyltransferase 3A (DNMT3A) mutation in cytogenetically normal patient population with acute myeloid leukemia (AML) determines prognosis with standard indication and consolidation therapy, as a guide to choosing alternative treatment if appropriate

Target Population

Acute myeloid leukemia (AML) patients with a normal cytogenetic profile

Interventions and Practices Considered

Deoxyribonucleic acid (DNA) methyltransferase 3A (DNMT3A) mutation testing

Major Outcomes Considered

- Overall survival
- Disease-free survival
- Relapse-free survival
- Event-free survival
- Complete remission

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The primary search is up to date as of July 26, 2012. Published literature was retrieved via searching the following electronic databases: MEDLINE (1946 to July Week 3, 2012) with in-process records and other non-indexed citations and daily updates via Ovid (July 25, 2012); EMBASE (1980 to Week 29, 2012) via Ovid; and The Cochrane Central Register of Controlled Trials (2012, Issue 7) via Ovid. Terms used were related to AML (acute myeloid leukemia OR acute myelogenous leukemia OR acute myelocytic leukemia) and DNMT3A (DNA methyltransferase 3A OR DNA [cytosine-5]-methyltransferase 3A human OR DNMT3A protein).

Study Selection Criteria and Protocol

Studies must have included cytogenetically normal (CN) patients stratified to the intermediate-risk group. Pediatric AML was not included for analysis (<15 years of age); no upper age limit was specified. Comparators under investigation were normal cytogenetic risk groups defined with the DNMT3A mutation versus normal cytogenetic risk groups without the DNMT3A mutation (wild type). The exact nature of the treatment administered was not of primary interest but was documented if the study provided the information. Primary outcomes of interest include overall survival (OS), complete remission (CR), cumulative incidence of relapse (CIR) and relapse-free survival (RFS). Co-occurring molecular aberrations, along with where the mutation was located in the gene, were documented for further research. Inclusion criteria encompassed systematic reviews, meta-analyses, clinical practice guidelines, randomized control trials, cohort studies (prospective and retrospective) or case-control studies with an analysis or subgroup analysis of DNMT3A biomarker status and investigated DNMT3A in patients with previously treated or untreated AML. Exclusion criteria was applied to articles published in a language other than English, were non-systematic reviews, letters, editorials, commentaries, or historical articles, or if patients had secondary AML.

Number of Source Documents

- Eight studies met the inclusion criteria and were included in the review.
- Six of the eight studies were included in quantitative synthesis (metaâ€analysis).

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

One reviewer went through the various databases that were mentioned in the search strategy (see the "Description of Methods Used to Collect/Select the Evidence" field) to identify relevant guidelines and articles. The same reviewer conducted title and abstract screening, and duplicates were removed. For each eligible study, the same reviewer would extract all the study data (including study design features, patient population, interventions, molecular exons sequenced and analyzed, co-occurring molecular aberrations with deoxyribonucleic acid [DNA] methyltransferase 3A [DNMT3A], and clinical outcomes).

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager software. For time-to-event outcomes, hazard ratios (HRs), rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al., 1998. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in Review Manager, would be used.

Statistical heterogeneity would be calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

Meta-analysis

The response data from six of the eight studies were pooled for a meta-analysis. See Figure 1 in the original guideline document for forest plot of effect size for overall survival.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

Almost all Program in Evidence-based Care (PEBC) documents undergo internal review. With recommendation reports, this review is conducted by the Director of the PEBC. The Working Group is responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by prospective and retrospective studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Assessing deoxyribonucleic acid (DNA) methyltransferase 3A (DNMT3A) mutational status provides important prognostic information for acute myeloid leukemia (AML) patients with a normal karyotype.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- The recommendation is based on evidence currently available. Despite the heterogeneous nature of the studies included, the likelihood of having a series of large homogenous studies done in this patient population is low due to the nature of the disease and its management.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Nov 27

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Molecular Oncology Advisory Committee

Composition of Group That Authored the Guideline

Authors: B. Leber, N. Ismaila, S. Kamel-Reid, M. Rutherford

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Molecular Oncology Advisory Committee (MOAC) members, and internal and external reviewers were asked to disclose potential conflicts of interest.

The authors, members, and reviewers reported that they had no conflicts of interest.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- The prognostic value of the DNMT3A biomarker in cytogenetically normal patients with acute myeloid leukemia. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2013 Nov 27. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available in PDF from the Cancer Care Ontario Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 10, 2014.

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